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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte IRA H. PASTAN, TAPAN K. BERA, PAUL E. KENNEDY,
EDWARD A. BERGER, and CARLOS F. BARBAS, III

Appeal 2009-003719
Application 09/673,707
Technology Center 1600

Decided: January 15, 2010

Before TONI R. SCHEINER, DEMETRA J. MILLS, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness and indefiniteness. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF CASE

The following claim is representative.

1. An immunotoxin comprising a cytotoxin attached to an anti-gp120 antibody having the binding specificity to the CD4 binding site of gp120 of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2) and a minimum binding affinity to gp-120 of 3B3 Fv (which 3B3 Fv consists of a VH chain and a VL chain as encoded by SEQ ID NO.:2), wherein said immunotoxin specifically binds to and kills mammalian cells infected with HIV- 1.

Cited References

Pastan et al. US 5,458,878 Oct. 17, 1995

Matsushita et al., *Selective Killing of HIV-Infected Cells by Anti-gp120 Immunotoxins*, 6 AIDS RESEARCH AND HUMAN RETROVIRUSES 192-203 (1990).

Barbas et al., *In vitro evolution of a neutralizing human antibody to human immunodeficiency virus type 1 to enhance affinity and broaden strain cross-reactivity*, 91 PROC. NATL. ACAD. SCI. USA 3809-3813 (1994).

Ramachandran et al., *Failure of short-term DC4-PE40 infusions to reduce virus load in human immunodeficiency virus-infected persons*, 170 J. INFECT. DIS. 1009-1013 (1994).

Davey et al., *Use of recombinant soluble CD4 Pseudomonas exotoxin, a novel immunotoxin, for treatment of person infected with human immunodeficiency virus*, 170 J. INFECT. DIS. 1180-1188 (1994).

Berger et al., *Reconsidering targeted toxins to eliminate HIV infection: You gotta have HAART*, 95 PROC. NATL. ACAD. SCI. USA 11511-11513 (1998).

Goldstein et al., *Chimeric Toxins Targeted to the Human Immunodeficiency Virus Type 1 Envelope Glycoprotein Augment the In Vivo Activity of Combination Antiretroviral Therapy in thy/liv-SCID-Hu Mice*, 181 J. INFECT. DIS. 921-926 (2000).

Declaration of Dr. David J. Fitzgerald, dated October 13, 2006.

Grounds of Rejection

1. Claims 1-6, 9, 11, 52-55, 57, 68-72, 74-75 and 77 are rejected under 35 U.S.C. § 103(a) as obvious over Matsushita, Barbas and Pastan.

2. Claims 1-7, 9, 11, 52, 55, 57, 68-75 and 77 are rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. [1]

FINDINGS OF FACT

1. The Examiner finds that Matsushita et al. disclose anti-gp120 immunotoxins comprising the 0.5β antibody coupled to the *Pseudomonas* exotoxin (see abstract).

2. "Matsushita et al. differs from the instant invention in that they don't disclose the use of the 3B3 antibody or the use of altered PE40." (Ans. 4.)

3. "Barbas et al. disclose a human antibody to gp120 (3B3) with broad strain cross-reactivity (see page 3812-3813)." (*Id.*)

4. "Pastan et al. disclose modifications of the carboxyl terminus of the PE molecule resulting in increased cytotoxicity (see abstract and column 3, line 27 to column 4, line 10)." (*Id.*)

5. The Examiner finds that, given that "Matsushita et al. suggest the use of an antibody that is broadly reactive with a number of HIV isolates (see page 200), it would have been obvious for one of ordinary skill in the art to use the 3B3 antibody in the immunotoxin disclosed by Matsushita et al." (*Id.*)

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[1] We note that the Examiner has indicated the indefiniteness rejection set forth in the Final Rejection, page 7 was not presented for review in the Brief (Ans. 3). However this rejection was addressed in the Brief on pages 25-27, and Reply Br. 2, and is before us on Appeal.

6. The Examiner further finds that, "it would a have been equally obvious for one of ordinary skill to incorporate the PE modifications disclosed by Pastan et al. in order to take advantage of the resulting increase in cytotoxicity." (Ans. 4.)

7. The Examiner finds that,

> [W]hile the incorporation of immunotoxins in kits is not explicitly disclosed by Matsushita et al., said incorporation would have been obvious to one of ordinary skill in the art in order to reduce cost and ease preparation time. It should be noted that while the sequence of the 3B3 antibody is not explicitly disclosed, it is deemed in absence of evidence to the contrary to be the same as that of the 3B3 of the instant application (SEQ ID NO: 1).

(*Id.* at 4-5.)

8. The Examiner finds that, "given that the anti-gp 120 immunotoxins is well known in the art yielding predictable results, it is obvious for the skilled artisan to utilize any known anti-gp 120." (*Id.* at 5.)

9. "Ramachandran et al. and Davey et al. disclose the failure of the CD4-PE40 and sCD4-PE40 in clinical trials." (*Id.*)

10. The Examiner's position is that the CD4-PE immunotoxins and the Matsushita "immunotoxins are not analogous and that the success of the gp120-PE immunotoxin disclosed by Matsushita would carry more weight with the skilled artisan than the failure of a non-analogous immunotoxin. The Appellant's arguments are based on the fact that both the anti-gpl20- PE and the CD4-PE immunotoxins will bind to cells expressing gp120 (i.e. HIV-1 infected cells)." (*Id.*)

11. The Examiner finds that "the Appellant has ignored the fact that while both immunotoxins may bind to cells expressing gp120, the CD4-PE

immunotoxin would also bind to all of the natural ligands of CD4 (e.g. IL16 etc.) thereby affecting untold cellular processes and endocrine cascades." (Ans. 6.)

12. CD4 designates a biochemical receptor found on the surface of various cells, esp. helper T cells: HIV binds to this receptor.

http://www.yourdictionary.com/cd4

13. According to the Specification,

> The parental antibody from which 3B3 was derived, was isolated from a combinatorial phage display library constructed from bone marrow RNA of an infected individual (Burton *et al.* (1991) *Proc. Natl. Acad. Sci. USA*, 88: 10134-10137). While there is a high degree of inter-isolate sequence variability of gp120, the 3B3 antibodies of this invention reacts with the conserved CD4-binding site of gp120, the external subunit of the envelope glycoprotein (Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA*, 91: 3809-3813).

(Spec. 11.)

14. The Specification states that "unlike other monoclonal antibodies that are also directed to CD4 binding epitope, the parent of the 3B3 antibody can neutralize many different laboratory strains of HIV-1 as well as many primary isolates (Kessler *et al.* (1997) *Hum. Retrovinises* 13: 575-582; Burton *et al.* (1994) *Science* 266: 1024-1027; Trkola *et al.* (1995) *J. Virol.*, 69: 6609-6617)." (*Id.*)

15. "Dr. Fitzgerald declared that those of skill in the art would consider the immunotoxins of the instant invention analogous, *in terms of the cells they were intended to bind,* to the immunotoxins of Ramachandran and Davey" as they both bond to cells infected with HIV1. (Fitzgerald Declaration, paragraph 15; Ans. 8.)

16. Dr. Fitzgerald's Declaration demonstrated that PE based toxins would not bind to healthy cells and that both the CD4-PE and the Matsushita immunotoxins would bind to the same cells. (Ans. 8.)

17. Dr. Fitzgerald states that CD4 has interactions with major histocompatibility class 2 molecules. (Fitzgerald Declaration ¶ 16.) CD 4 does not bind to any cell expressing CD4 on its surface. (Fitzgerald Declaration ¶ 17.)

ISSUE

The Examiner argues that, "[g]iven that Matsushita et al. suggest the use of an antibody that is broadly reactive with a number of HIV isolates (see page 200), it would have been obvious for one of ordinary skill in the art to use the 3B3 antibody [of Barbas] in the immunotoxin disclosed by Matsushita et al." The Examiner further finds that, "it would a have been equally obvious for one of ordinary skill to incorporate the PE modifications disclosed by Pastan et al. in order to take advantage of the resulting increase in cytotoxicity." (Ans. 4.)

Appellants contend that "[t]he rejection's reliance on the Matsushita reference as providing motivation to the person of skill to create the immunotoxins of the present invention is misplaced." (App. Br. 8.) Appellants argue that the Examiner

> [F]ails to give proper weight to, all of the information available to the person of skill at the time the invention was made. That information includes the results of two clinical trials of toxins targeted to the HIV gp120 glycoprotein, and evidence of record as to how persons of skill responded to those results: Following the publication of the Matsushita reference, two anti-gp120 conjugates went into clinical trials, and both failed.

(*Id.*)

The issue is: Have Appellants demonstrated error in the Examiner's prima facie case of obviousness and has the Examiner given proper weight to failed clinical trials after the date of the Matsushita reference? Is there motivation to modify the Matsushita immunotoxins?

PRINCIPLES OF LAW

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie case of obviousness has been established, we considered the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

"[O]bviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away

if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

"The fact that the motivating benefit comes at the expense of another benefit … should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another. Instead, the benefits, both lost and gained, should be weighed against one another." *Medichem S.A. v. Rolabo S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

As to motivation to combine, the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), rejected a rigid application of the teaching-suggestion-motivation test. The Court recognized that it is often necessary to look at the interrelated teaches of multiple references; the effects of demands of the marketplace; and the background knowledge possessed by a person of ordinary skill, "all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." *Id.* at 418. Moreover, the "obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents." *Id.* at 419. Finally, one "of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims." *Id.* at 419-420.

ANALYSIS

Appellants contend that the obviousness rejection's reliance on the Matsushita reference as providing motivation to the person of skill to create

the immunotoxins of the present invention is misplaced. Appellants argue that the Examiner fails to give proper weight to the failure of two clinical trials of two anti-gp120 conjugate toxins targeted to the HIV gp120 glycoprotein. In particular, the Appellants argue that Ramachandran and Davey used CD4-PE40 conjugates which bind to gp120, and found the conjugates to be toxic to the liver. (App. Br. 8.) Appellants argue that the CD4-PE conjugates and those of Matsushita bind to the same cells, and therefore one of ordinary skill in the art would have been dissuaded by the failure of the CD4-PE conjugates. Appellants argue that Goldstein and Berger evidence how persons of ordinary skill in the art responded to the failed clinical trials, suggesting that the approach of using anti-HIV antibodies as targeting moieties for anti-HIV immunotoxins had been abandoned. (App. Br. 9.)

We are not persuaded. We acknowledge that the Declaration of Dr. Fitzgerald states that the CD4-PE and the Matsushita immunotoxins bind to the same cells and that he concludes that these conjugates are analogous. However, we do not find that Appellants have established with appropriate evidence that the CD4-PE conjugates and those of Matsushita have the same specificity. To the contrary, evidence of record suggests that gp120 immunotoxins have a different specificity, affinity and neutralization capabilities as compared to CD4-PE immunotoxins. (Barbas, page 3811.) For example, "unlike other monoclonal antibodies that are also directed to CD4 binding epitope, the parent of the 3B3 antibody can neutralize many different laboratory strains of HIV-1 as well as many primary isolates." (Spec. 11.) Dr. Fitzgerald states that CD4 has interactions with major histocompatibility class 2 molecules (Fitzgerald Declaration ¶ 16) and that

CD4 does not bind to any cell expressing CD4 on its surface (*id.* at¶ 17). The monoclonal antibody of Matsushita is directed against an external envelope glycoprotein (gp120) of HIV. Thus, we do not find that Appellants have shown that the specificities of CD4 and the gp120 directed antibody, 3B3, are the same in a manner which would make one of ordinary skill in the art consider the two antibodies to be analogous, thereby teaching away from the use of the Matsushita gp120 antibodies in a conjugate.

Appellants argue that Berger stated that high hopes were dashed in the Phase I clinical trials and the clinical program was terminated. (App. Br. 9.) However, Berger also indicated, that prior to the filing date of the present application hepatotoxicity was found not to be a general property of PE derivatives in humans, citing L.H. Pai, et al., *Nat. Med.* 2 p. 350-353 (1996). (Berger 11512, first column), and that the hepatotoxicity CD4-PE40 might have been associated with viral load.

In addition, it is well known that many medicinal compounds have unwanted side effects. It is well recognized that "[t]he fact that the motivating benefit comes at the expense of another benefit … should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another. Instead, the benefits, both lost and gained, should be weighed against one another." *Medichem S.A. v. Rolabo S.L.,* 437 F.3d 1157, 1165 (Fed. Cir. 2006). Thus we do not find that one of ordinary skill in the art would consider the toxicity of CD4-PE conjugates alone would have discouraged the use of analogous conjugates.

Since Appellants have not shown that the antibodies share analogous specificities and properties and Appellants have not shown that Matsushita would represent a teaching away in view of clinical trials of record, we agree

with the Examiner that the success of the gp120-PE immunotoxin of Matsushita would carry some weight with the skilled artisan. (Ans. 6.) The Examiner further finds that "the failure of the CD4 based immunotoxins in clinical trials would motivate, not discourage the skilled artisan to improve on the gp120 based immunotoxin of Matsushita." (*Id.*)

Further contrary to Appellants' position, Goldstein did not indicate that using anti-HIV antibodies as targeting moieties for anti-HIV immunotoxins had been abandoned by those of ordinary skill in the art, only that the clinical trials with CD4-PE40 were abandoned.[2] If Goldstein is to be relied on for its negative teachings, it is also available for its teachings to those of ordinary skill in the art as a whole. Goldstein concluded that while CD4-PE conjugates showed hepatotoxicity in humans, immunotoxins such as 3b3(Fv)-PE38 should not be problematic, particularly in view of the absence of severe hepatotoxicity with other PE-based antitumor immunotoxins in phase I trials. (Goldstein, p. 925, col. 2.) Thus, Goldstein would reasonably appear to support the position of the Examiner that the failed CD4-PE conjugates of the clinical trials are not analogous to the gp120-PE conjugates of Matsushita.

Therefore, contrary to Applicant's assertion, we find that the evidence of record suggests that the gp120-PE and the CD4-PE immunotoxins are not equivalent, and thus the failed clinical trials with CD4-PE do not provide a teaching away to those of ordinary skill in the art. Moreover, the failure of the CD4 based immunotoxins in clinical trials would not, by itself, constitute

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[2] See discussion of Berger, herein.

a teaching away from using similar conjugates, when other benefits are present.

As to the basis of the obviousness rejection, Matsushita teaches anti-gp120 immunotoxins comprising the 0.5β antibody coupled to the *Pseudomonas* exotoxin (see abstract). "Matsushita et al. differs from the instant invention in that they don't disclose the use of the 3B3 antibody or the use of altered PE40. Barbas et al. disclose a human antibody to gp120 (3B3) with broad strain cross-reactivity (see page 3812-3813)" and thus motivates one of ordinary skill in the art to use an antibody with broad HIV strain cross reactivity. "Pastan et al. disclose desireable modifications of the carboxyl terminus of the PE molecule resulting in increased cytotoxicity (see abstract and column 3, line 27 to column 4, line 10)." (Ans. 4.)

We agree with the Examiner that the cited references provide sufficient motivation to substitute the human antibody to gp120 (3B3) with broad strain cross-reactivity of Barbas for the gp120 antibody of Matsushita, and motivation to incorporate the PE modifications disclosed by Pastan et al. in order to take advantage of the resulting increase in cytotoxicity.

We do not find that Appellants have provided sufficient rebuttal evidence to defeat this motivation, or provided evidence to defeat the Examiner's prima facie case.

CONCLUSION OF LAW

Appellants have not demonstrated error in the Examiner's prima facie case of obviousness, the Examiner given proper weight to failed clinical trials after the date of the Matsushita reference. The Examiner has shown

sufficient motivation in the cited references to modify the Matsushita immunotoxins.

2. Claims 1-7, 9, 11, 52, 55, 57, 68-75 and 77 are rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. (Final Rej. 7.)

This rejection was not addressed in the Answer, as the Examiner believed Appellants did not respond to this rejection. (Ans. 3.) Moreover, the Examiner appears to have changed the claims involved in this rejection. (*Id.*)

The Examiner argues that claims 1, 52, 68 and 74 are indefinite due to the use of the phrase "which 3B3 Fv consists of a VH chain and a VL chain encoded by SEQ ID NO:2." (*Id.*) The Examiner argues that it is unclear whether Applicant is stating that both the VH and VL chains are encompassed by SEQ ID NO:2 or both the VH and VL are individually encoded by SEQ ID NO:2.

Appellants contend that

> Persons of skill claim reviewing the sequence listing of the subject application disclosure will see the following description for SEQ ID NO.:2: "Description of Artificial Sequence: 3B3V-H(G1y-4Ser)-3V-L nucleotide sequence". See, Sequence Listing dated December 5,2002. Accordingly, the content of the application disclosure informs the person of skill in the art that SEQ ID NO.:2 is a nucleotide sequence encoding first the 3B3 VH chain, a linker, and then the 3B3 VL chain. Any person of skill concerned about the claim language would turn to the end of the patent, see the sequence description for SEQ ID NO.:2, and immediately understand exactly what the sequence encodes. Applicants also respectfully note that the persons of skill in this art are typically Ph.D. level scientists who can be presumed to understand the straightforward description set forth in the sequence listing.

(App. Br. 26.) Appellants argue that the alternative claim readings are not "permissible in light of the application disclosure." (*Id.* at 27.)

We do not find that the Examiner has indicated why the claim language is indefinite in view of the Specification. We therefore, agree with Appellants' argument and the indefiniteness rejection is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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